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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
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1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,574	ISNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2009 and 29 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-61,63-66,68-70,72 and 76-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-61, 63-66, 68-70, 72 and 76-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/29/09 and supplemental amendment filed on 3/17/09 were entered.

Amended claims 49-61, 63-66, 68-70, 72 and new claims 76-81 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 49-61, 63-66, 68-70, 72 and new claims 76-81 are still rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Hammond et al. (US Patent 5,880,090; IDS). ***This is a***

slightly modified rejection necessitated by Applicant's amendment to accommodate new claims 79-81.

It is noted that the teachings of Isner (WO 97/14307) and Isner (US 6,121,246) are identical. For simplification, only the teachings of Isner (WO 97/14307) will be discussed in details below. Isner (WO 97/14307) teaches a method for enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal having cerebrovascular ischemia, renal ischemia, pulmonary ischemia, limb ischemia, ischemic cardiomyopathy and myocardial ischemia (page 4, lines 5-23). The method comprises the step of injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein by any injection means, and the nucleic acid may be carried by vehicles such as cationic liposomes, adenoviral vectors and that nucleic acid encoding different angiogenic proteins may be used separately or simultaneously (page 4, line 25 continues to line 8 of page 5). Angiogenic protein includes aFGF, bFGF, VEGF (including VEGF165, see page 15, line 19), EGF, PDGF, PD-ECGF, HGF, colony stimulating factor (CSF), macrophage-CSF (M-CSF), granulocyte/macrophage CSF (GM-CSF) and nitric oxidesynthase or muteins or portions thereof (page 5, lines 10-22). Isner (WO 97/14307) also teaches that the nucleic acid encoding an angiogenic protein is inserted into a cassette where it is operably linked to a promoter that is capable of driving expression of the protein in cells of the desired target tissue (page 9, line 28 continues to line 20 of page 10). **Isner (WO 97/14307) further teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing**

angiogenesis, including, for example, nitric oxide synthase, L-arginine, fibronectin, urokinase, plasminogen activator and heparin (page 11, lines 15-19). Isner (WO 97/14307) also discloses that catheters have been used for gene delivered in the art (page 1, line 23 continues to line 30 of page 2).

Isner (WO 97/14307) or Isner (US 6,121,246) does not specifically teach the administration of an effective amount of a GM-CSF or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, including the administration of GM-CSF one week prior to administration of the nucleic acid; **even though the reference teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.**

At the effective filing date of the present application Hammond et al already taught that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient (see at least Summary of the invention). Hammond et al also note that CD34+ circulating cells in the blood can participate in the repair of ischemic tissue (col. 3, lines 28-37); and that the endothelialization-promoting agent can be administered by any route of delivery, including intravenous delivery (col. 4, lines 24-35). Hammond et al further disclose that the endothelialization-promoting agent may be administered once daily for one to 14

days, and the first dose may be administered as much as seven days prior to the implantation of a synthetic vascular graft in a patient in need thereof or may begin on the same day as graft implantation (col. 4, lines 24-45).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of either Isner (WO 97/14307) or Isner (US 6,121,246) by further administering to the treated mammal an effective amount of GM-CSF or an effective fragment thereof, including via an intravenous delivery and administering at least GM-CSF one week prior to the administration of a nucleic acid encoding an angiogenic protein or an effective fragment thereof, in light of the teachings of Hammond et al, and since either Isner (WO 97/14307) or Isner (US 6,121,246) also teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modifications because Hammond et al. already demonstrated that cytokines such as stem cell factor (SCF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for increasing endothelialization in a treated patient, including their administration as much as seven days prior to another treatment (e.g., implantation of a vascular graft) in a patient in need thereof; and this mobilization of endothelial cell progenitors would further enhancing blood vessel formation or angiogenesis in an ischemic tissue in a mammal

having a myocardial ischemia, and thus further optimizing the therapeutic outcome. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Isner (WO 97/14307) or Isner (US 6,121,246) and Hammond et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 1/29/09 (pages 7-10) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Once again, Applicants argue basically that the Examiner is not considering the Isner reference as a whole, particularly the rejection does not take into consideration **an essential element of the teachings of Isner of administration of the angiogenic agent directly to the ischemic tissue**. When taken as a whole, modification of Isner to include systemic administration as taught by Hammond would change the principle of operation of Isner and therefore the references can not be combined and the methods claimed in the instant application can not be *prima facie* obvious in view of the cited references. Applicants also argue previously that systemic

administration was clearly known at the time of the filing of the Isner reference, however, systemic administration of agents presumably was insufficient to provide the high and local concentration of angiogenic agents over time that was required for the treatment of ischemia; and **the invention described in the Isner reference was made to overcome limitation in the prior art regarding the limitation of treatment methods which require the repeated doses of angiogenic proteins by intracellular administration over a range of 10 to 14 days; and therefore the Isner reference must be understood as teaching away from systemic administration of angiogenic agents**. With respect to new claims 76-78 in which the method results in an increase in neovascularization from 50% to 300% in the ischemic tissue, Applicants further argue that there can be no reason to expect such a high level of neovascularization based on the combined teachings of Isner and Hammond, and that neither of the references teaches or suggests the timing of administration of various factors (limitation of new claims 79-81).

Firstly, the essential element of a method for inducing the formation of a new blood vessels in an ischemic muscle tissue, including ischemic myocardial muscle tissue, in a human host **comprises or includes** the step of directly injecting into said tissue of said human host an effective amount of a DNA sequence encoding an angiogenic protein (see Summary of the Invention and claims). **The modified method as a result of combining the teachings of Isner and Hammond as set forth above still contains this essential element of Isner, particularly to meet the limitation of step b) of the instant claims**. **Nowhere in the Isner reference that teaches**

explicitly that encoded gene products (not in the form of a vector or DNA or RNA), such as the angiogenic protein nitric oxide synthase, must be administered directly to ischemic tissue and that they should not be administered systemically when they are used in combination with an angiogenic factor in the form of a plasmid or a viral vector or DNA to enhance the activity of targeted cells (page 11, lines 11-19). It should be noted that an angiogenic factor in the form of a plasmid or a viral vector or DNA **must be directly administered to the target ischemic tissue in order to attain a desired therapeutic effect** due to the lack of in vivo vector targeting. However, **an angiogenic factor in the form of a protein and/or peptide is not necessarily required to be administered directly to the ischemic tissue in order to attain a desired therapeutic effect**. Isner states clearly "**Recent investigations have established the feasibility of using recombinant formulations of such angiogenic growth factors to expedite and/or augment collateral artery development in animal models of myocardial and hindlimb ischemia**" (page 8, first paragraph); and "**In addition, therapeutic angiogenesis has been achieved in the same or closely related models following administration of recombinant endothelial cell growth factor (ECGF) (Pu, et al., Circulation, 88:208-215 (1993)) and VEGF (Takeshita et al., Circulation, 90:228-234 (1994) supra). Previous studies, employing the animal model of chronic limb ischemia, demonstrated an efficacy of intra-muscular endothelial cell growth factor (ECGF) (Pu, et al., Circulation, 88:208-215 (1993)) or VEGF (Takeshita, et al., Circulation, 90:228-234 (1994) supra) administration**" (page 8, second full paragraph). The cited statement in the Isner "In studies with

recombinant angiogenic growth factors, intra-muscular administration of the growth factor was repeated over a range of 10 to 14 days. Thus, one major limitation of recombinant protein therapy is **its potential requirement** to maintain an optimally high and local concentration over time" (page 1, bottom of second paragraph) does not indicate or suggest in any shape or form that therapeutic angiogenesis would not be obtained via a systemic delivery of a recombinant angiogenic growth factor. Furthermore, it should also be noted that Isner teaches clearly that "If necessary, the nucleic acid may be reinjected to provide additional expression of the angiogenic protein" (page 5, lines 1-2). **This statement indicates clearly that the method of Isner can involve repeated doses or repeated injections to provide additional expression of an angiogenic protein**.

Secondly, Isner teaches clearly that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells in a method for enhancing blood vessel formation or an angiogenesis in an ischemic tissue, including ischemic cardiomyopathy or myocardial ischemia, in a mammal. Hammond et al. teaches clearly that SCF, GM-CSF, G-CSF are capable of mobilizing bone-marrow derived endothelial cell progenitors or non-adherent CD34+ cells in the blood for enhancing the endothelialization of synthetic vascular grafts in a patient. **Hammond also notes that CD34+ circulating cells in blood can participate in the repair of ischemic tissue** (col. 3, lines 28-37). Furthermore, **the circulating CD34+ or Flk-1+ cells can participate in the repair of ischemic tissue as proposed by Asahara et al. as evidenced at least by the results reported in the article of Science 275:965-967,**

1997 (This reference is specifically cited by Hammond et al.). The results showed that the EC progenitors can be incorporated into sites of active angiogenesis in animal models of ischemia. As already pointed out in the above rejection, an ordinary skilled artisan would have been motivated to modify the method of Isner by further administering to the treated mammal with an effective amount of at least one of SCF, GM-CSF and G-CSF, or an effective fragment thereof including via an intravenous delivery and administering at least GM-CSF one week prior to the administration of a nucleic acid encoding an angiogenic protein or an effective fragment thereof because Hammond already demonstrated that the aforementioned cytokines are capable of mobilizing bone-marrow derived endothelial cell progenitors in the blood and that their administration can be applied as much as seven days prior to another treatment (e.g., implantation of a vascular graft) in a patient in need thereof, and that this mobilization of endothelial cell progenitors would further enhance blood vessel formation or angiogenesis in an ischemic tissue in a mammal having a myocardial ischemia, and thus further optimizing the angiogenic therapeutic outcome.

Thirdly, with respect to the limitation "an increase in neovascularization from 50% to 300% in the ischemic tissue" of new claims 76-78, there is nothing unexpected about this recited result particularly at least on the use of a nucleic acid encoding a very potent angiogenic VEGF factor along with the mobilization of CD34+ circulating cells mediated by co-administered GM-CSF, let alone taking account of additional and/or synergistic effects endowed by co-administration of various angiogenic factors into a patient.

Amended claims 49-61, 63-66, 68-70, 72 and new claims 76-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) and Pierce et al (US 6,689,351 with an effective filing date of at least 2/22/1991). ***This is a modified rejection necessitated by Applicant's amendment.***

It is noted that the teachings of Isner (WO 97/14307) and Isner (US 6,121,246) are identical. For simplification, only the teachings of Isner (WO 97/14307) will only be discussed. The teachings of Isner (WO 97/14307) have been presented above. However, Isner (WO 97/14307) or Isner (US 6,121,246) does not specifically teach a systemical administration of an effective amount of a GM-CSF or an effective fragment thereof into the mammal with an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof, even though either one of the Isner references teaches that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells.

At the effective filing date of the present application Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see at least abstract; Methods; Table IV; page 994, col. 1, first paragraph; col. 2, first full paragraph).

Additionally, Pierce et al. already taught at least that GM-CSF is administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals (see at least col. 5, line 55 continues to line 27 of col. 6; Summary of the Invention, particularly col. 10, lines 7-8, lines 52-55; col. 12, lines 1-2).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of either Isner (WO 97/14307) or Isner (US 6,121,246) by utilizing recombinant G-CSF and/or GM-CSF as an endothelial cell mitogen to be systemically administered (e.g., intravenous administration) to a patient in need thereof in light of the teachings of Bussolino et al, and Pierce et al. and since either one of the Isner references already teaches that **an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells**, including nitric oxide synthase which is also an angiogenic protein or factor (page 11, lines 15-19; and page 7, lines 16-24).

An ordinary skilled artisan would have been motivated to carry out the above modifications because Bussolino et al. already demonstrated by exemplification that at least recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF or GM-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. Additionally, Pierce et al

already taught that that GM-CSF is routinely and successfully administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals. The modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Isner (WO 97/14307) or Isner (US 6,121,246) and Bussolino et al. and Pierce et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicants' arguments related to the above rejection in the Amendment filed on 1/29/09 (pages 10-11) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Once again, Applicants argue basically that the essential element of the teaching of Isner of administration of the angiogenic agent directly to the ischemic tissue, and when taken as a whole, modification of Isner to include systemic administration would change the principle of operation of Isner; and therefore the combination of the references is not obvious.

Please refer to the examiner's responses to the same Applicant's line of arguments in the rejection of claims 49-61, 63-66, 68-70, 72 and new claims 76-81 under 35 U.S.C. 103(a) as being unpatentable over either Isner (WO 97/14307) or Isner (US 6,121,246; IDS) in view of Hammond et al. (US Patent 5,880,090; IDS) above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 49-61, 63-66, 68-70, 72 and new claims 76-78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,121,246 in view of Bussolino et al. (J. Clin. Invest. 87:986-995, 1991; IDS) and Pierce et al (US 6,689,351). ***This is a slightly modified rejection necessitated by Applicant's amendment.***

The instant claims are directed to a method for treating ischemic myocardial tissue of a mammal in need of such a treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an

effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount granulocyte macrophage colony stimulating factor (GM-CSF) or an effective fragment thereof, thereby treating the ischemic myocardial tissue of the mammal, wherein the GM-CSF or an effective fragment thereof is administered systemically.

Claims 1-15 of U.S. Patent No. 6,121,246 are drawn to a method for inducing the formation of new blood vessels in an ischemic tissue in a human host, **comprising**: a) selecting a human host in need of increased blood flow in an ischemic muscle tissue, and (b) directly injecting into said tissue of said human host an effective amount of a DNA sequence encoding an angiogenic protein or a modified angiogenic protein, wherein said DNA sequence comprises a promoter sequence and either a native secretory signal sequence or an operably linked secretory signal sequence, wherein the angiogenic protein or modified angiogenic protein is selected from the group consisting of acidic and basic fibroblast growth factors, vascular endothelial growth factor, endothelial cell growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived endothelial growth factor, tumor necrosis factor alpha, hepatocyte growth factor, and insulin-like growth factor, and wherein said effective amount of said DNA sequence expresses sufficient angiogenic protein in said tissue to induce new blood vessel formation in said human host.

The claims of the present application differ from the claims of the issued US patent 6,121,246 in reciting treating ischemic myocardial tissue of a mammal in need

and further containing the additional step of systemically administering to the mammal an effective amount of GM-CSF or an effective fragment thereof.

It is noted that the term "ischemic muscle tissue" in US patent 6,121, 246 encompasses ischemic cardiomyopathy and myocardial ischemia (col. 2, lines 54-61). Additionally, with respect to the open language of the term "comprising" in the claimed method of issued US patent 6,121,246; the patent discloses specifically that an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously inducing angiogenesis, including, for example, nitric oxide synthase (an angiogenic protein) and others (col. 6, lines 4-14).

At the effective filing date of the present application, Bussolino et al already demonstrated that human recombinant G-CSF and GM-CSF are capable of inducing endothelial cells to proliferate and migrate *in vitro*, as well as repair of mechanically wounded endothelial monolayers, with an exemplification showing that recombinant G-CSF has also angiogenic activity *in vivo*. Additionally, recombinant G-CSF exhibits synergistic effects with bFGF in inducing *in vivo* angiogenesis (see abstract and Methods).

Additionally, Pierce et al. already taught at least that GM-CSF is administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals (see at least col. 5, line 55 continues to line 27 of col. 6; Summary of the Invention, particularly col. 10, lines 7-8, lines 52-55; col. 12, lines 1-2).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time the invention was made to modify the claims of the issued US patent 6,121,246 by further administering to a human host in need thereof, including a human host suffering myocardial ischemia, with an effective amount of GM-CSF or an effective amount thereof, including via a systemic delivery route such as intravenous administration in light of the teachings of Bussolino et al and Pierce et al.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Bussolino et al. already demonstrated by exemplification that at least recombinant G-CSF has angiogenic activity *in vivo*, and that it also exhibits synergistic effects with at least another endothelial cell mitogen bFGF in inducing *in vivo* angiogenesis. This would in effect optimize the desired therapeutic outcome. The synergistic effects in the induction of angiogenesis would also be reasonably expected for the interaction between the administered G-CSF or GM-CSF and encoded bFGF or its fragment being expressed from a delivered nucleic acid. Additionally, Pierce et al also taught that that GM-CSF is routinely and successfully administered parenterally, including intravenous administration, for therapeutic uses including for promoting accelerated wound healing in mammals. Accordingly, the modified method is indistinguishable from the presently claimed method.

An ordinary skilled artisan would have a reasonable expectation of success in light of the issued claims in US patent 6,121,246, and the teachings of Bussolino et al. and Pierce et al., coupled with a high level of skill of an ordinary artisan in the relevant art.

Therefore, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Amended claims 49-59, 65, 68-70 and new claims 76-78 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 69 of copending Application No. 10/696,391 for the same reasons already set forth in the Office action mailed on 1/2/08 (pages 12-13). ***The same rejection is restated below.***

Although the conflicting claims are not identical, they are not patentably distinct from each other because a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment having the steps recited in independent claim 69 in the copending Application No. 10/696,391 anticipates the claimed genus of a method for treating ischemic myocardial tissue of a mammal in need of such treatment in the application being examined and, therefore, a patent to the genus would, necessarily, extend the rights of the species or sub- should the genus issue as a patent after the species of sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Amended claims 49-61, 63-66, 68-70, 72 and 76-78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49, 52, 54-56, 58-65 and 68 of copending Application No.

10/696,391. ***This is a slightly modified rejection necessitated by Applicant's amendment.***

Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are directed to a method for treating ischemic myocardial tissue of a mammal in need of such treatment comprising: a) identifying a mammal which has, is suspected of having, or will have the ischemic tissue; b) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and c) administering to the mammal an effective amount of a granulocyte macrophage colony GM-CSF or an effective fragment thereof, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, wherein the GM-CSF or an effective fragment thereof is administered systemically; whereas claims 49, 52, 54-56, 60-65 and 68 of copending Application No. 10/696,391 are drawn to a method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment comprising: a) injecting an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; b) administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, wherein the angiogenic factor or an effective fragment thereof is administered systemically, thereby inducing the new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells in the mammal, and (c) monitoring a cardiac function by the recited means, and wherein the method improves said cardiac function.

The claims of the present application differ from the claims of the copending Application No. 10/696,391 in reciting administering specifically to the mammal an effective amount of a granulocyte macrophage colony stimulating factor (GM-CSF) or an effective fragment thereof. The claims of the present application can not be considered to be patentably distinct over claims 49, 52, 54-56, 58-65 and 68 of copending Application No. 10/696,391 when there is a specific disclosed embodiment of the co-pending application that teaches that SCF, CSF including GM-CSF or their fragments are the angiogenic factors. Accordingly, the claims of the copending Application No. 10/696,391 fall within the scope of claims 49-61, 63-66, 68-70 and 72 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the method for inducing new blood vessel growth in myocardial tissue of a mammal in need of such treatment in the co-pending application by also utilizing SCF and/or CSF, including GM-CSF or fragments thereof as angiogenic factors that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these embodiments are explicitly disclosed in the co-pending application are preferred embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

It is noted that the above provisional double patenting rejections are not the only remaining rejections in the instant application.

Conclusions

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633